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Efficacy of cognitive bias modification interventions in anxiety and depressive disorders: a systematic review and network meta-analysis

Liviu A Fodor, Raluca Georgescu*, Pim Cuijpers, Ştefan Szamoskozi, Daniel David, Toshiaki A Furukawa, Ioana A Cristea*

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*Contributed equally

International Institute for The Advanced Studies of Psychotherapy and Applied Mental Health (L A Fodor MA, R Georgescu MA), **Evidence Based Psychological Assessment and Interventions Doctoral School** (L A Fodor, R Georgescu), **Department of Applied Psychology** (Prof Ş Szamoskozi PhD), **and Department of Clinical Psychology and Psychotherapy** (Prof D David PhD, I A Cristea PhD), **Babeş-Bolyai University, Cluj-Napoca, Romania; Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, Amsterdam, Netherlands** (Prof P Cuijpers PhD); **Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA** (Prof D David); **Department of Health Promotion and Human Behavior, School of Public Health in the Graduate School of Medicine, Kyoto University, Kyoto, Japan** (Prof T A Furukawa MD); **and Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy** (I A Cristea)

Correspondence to: Dr Ioana A Cristea, Department of Brain and Behavioral Sciences, University of Pavia, 27100 Pavia, Italy
ioana.cristea@unipv.it

Summary

Background Cognitive bias modification (CBM) therapies, including attention bias modification, interpretation bias modification, or approach and avoidance training, are prototypical examples of mechanistically derived treatments, but their effectiveness is contentious. We aimed to assess the relative effectiveness of various CBM interventions for anxious and depressive symptomatology.

Methods For this systematic review and network meta-analysis, we searched PubMed, PsycINFO, Embase, and Cochrane Central Register from database inception up until Feb 7, 2020. We included randomised controlled trials of CBM versus control conditions or other forms of CBM for adults aged 18 years and older with clinical or subclinical anxiety or depression measured with a diagnostic interview or a validated clinical scale. We excluded studies comparing CBM with a non-CBM active intervention. Two researchers independently selected studies and evaluated risk of bias with the Cochrane Collaboration tool. Primary outcomes encompassed anxiety and depressive symptoms measured with validated clinical scales. We computed standardised mean differences (SMDs) with a restricted maximum likelihood random effects model. This study is registered with PROSPERO, CRD42018086113.

Findings From 2125 records we selected 85 trials, 65 (n=3897) on anxiety and 20 (n=1116) on depression. In a well connected network of anxiety trials, interpretation bias modification outperformed waitlist (SMD –0·55, 95% CI –0·91 to –0·19) and sham training (SMD –0·30, –0·50 to –0·10) for the primary outcome. Attention bias modification showed benefits only in post-hoc sensitivity analyses excluding post-traumatic stress disorder trials. Prediction intervals for all findings were large, including an SMD of 0. Networks of depression trials displayed evidence of inconsistency. Only four randomised controlled trials had low risk of bias on all six domains assessed.

Interpretation CBM interventions showed consistent but small benefits; however heterogeneity and risk of bias undermine the reliability of these findings. Larger, definitive trials for interpretation bias modification for anxiety might be warranted, but insufficient evidence precludes conclusions for depression.

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Introduction

The current research agenda for psychological treatments recommends moving towards developing interventions mechanistically, by translating experimental findings.[1] Cognitive bias modification (CBM) interventions are prototypical examples. These encompass a diversity of approaches with multiple variants in each, such as attention bias modification (ABM), CMB-interpretation (CBMI), or approach and avoidance training. Across all methods, a target cognitive bias is manipulated, in which participants are taught (often without being explicitly made aware) to preferentially attend to, process, or otherwise engage with specific types of stimuli (ie, positive, neutral), while simultaneously avoiding others (ie, negative, threatening).[2] CBM interventions are appealing because of their accessibility and scalability, as they consist of brief sessions of a computer-based task, possibly administered online.

Nevertheless, the effectiveness of CBM interventions is contentious. Meta-analyses of randomised controlled trials often reached strikingly different conclusions. For the most investigated form—ABM for anxiety disorders—some meta-analyses reported small, frequently non-significant, symptom reductions compared with control conditions,[3,4] whereas others reported significant effects of larger magnitude.[5,6] There were fewer trials for depression, with mixed findings.[3,7]

The diversity of CBM procedures is mirrored by the use of various control groups, rendering the standard for gauging the effectiveness of CBM uncertain. For instance, because the tasks are computerised, usually not requiring participant awareness, several studies have used a control condition aimed to function as a placebo. This so-called no contingency or sham training control task is identical to the active intervention, except that no stimulus type is favoured—ie, positive or neutral stimuli

Research in context

Evidence before this study

We searched PubMed from database inception up to Jan 1, 2019, using the search "((cognitive bias) OR (attention* bias) OR (interpret* bias) AND (training or modification)) AND (anxiety disorder[MeSH Terms] OR anxiety[MeSH Terms] OR Trauma and Stressor Related Disorders[MeSH Terms] OR depressive disorder[MeSH Terms] OR depression[MeSH Terms]) AND (meta-analy*[Title/Abstract])". No language restrictions were imposed. We identified 64 records, of which 12 were meta-analyses including cognitive bias modification (CBM) interventions for clinically relevant outcomes related to depression or anxiety in adults. There was an additional overview of meta-analyses. Most meta-analyses focused on attention bias modification. For interpretation bias modification, the most recent meta-analysis included trials done up to 2013 and is probably outdated. Despite this proliferation, no clear answers emerged as to whether investment in CBM as a treatment is justified and the scientific community is polarised about how to move forward. Some researchers argue that CBM interventions have at best small and transient clinical benefits and hence translation to clinical trials has largely been unsuccessful. Yet others focus on more substantial benefits for various subgroups and support further investment in clinical trials. However, CBM is a heterogeneous family of interventions and it is possible that some forms have been more successfully translated than others.

Added value of this study

To our knowledge, we report the first network meta-analysis of CBM for clinically relevant outcomes, aggregating the largest number of trials to date. This methodology has the unique advantage of simultaneously drawing from direct and indirect comparisons and can therefore answer questions regarding relative effectiveness. Our findings across four network meta-analyses comprising 85 randomised trials in participants with anxious or depressive symptoms showed that one CBM intervention—interpretation bias modification—was consistently more effective than control conditions for symptoms of anxiety and depression in anxiety disorders. No reliable conclusions could be drawn for depressive disorders, because of inconsistency in the networks likely to be caused by the small number of direct comparisons.

Implications of all the available evidence

The notion of developing new treatments mechanistically, by identifying targets from experimental laboratory studies (ie, experimental psychopathology), is widely embraced as key in a programmatic new research agenda. CBM interventions represent a structured and consolidated attempt along these lines. Interpretation bias modification emerged as a promising treatment and could warrant large-scale testing, ensuring masking of participants and outcome assessors to avoid outcome reporting bias.

appear as frequently as negative ones. As with placebo, some studies reported benefits for participants randomly assigned to this control arm.[8] Furthermore, it is unclear whether some versions of CBM are more effective than others for specific symptoms.

Because of the scarcity of studies comparing versions of CBM with each other and with different control groups, these questions cannot be settled in a typical pairwise meta-analysis of direct comparisons. Network meta-analyses synthesise direct and indirect evidence, enabling the estimation of comparative effects even in the absence of trials directly comparing interventions.[9]

We therefore did a systematic review and network meta-analysis to establish the relative effectiveness of CBM procedures (ie, ABM, CBMI, approach and avoidance training), compared with each other and with control groups, for anxious and depressive symptomatology.

Methods

Search strategy and selection criteria

For this systematic review and network meta-analysis, we searched PubMed, PsycINFO, Embase, and Cochrane Central Register of Controlled Trials databases from database inception up until Feb 7, 2020, using the combinations of terms (both as controlled vocabulary thesaurus and free text) relating to "cognitive bias modification", "attention* bias modification", "attention* bias training", "interpret* bias modification", and "anx*", "fear", "depress*", "dysth*", "obsess*", "phob*", "panic", "agoraphob*", "PTSD", "post traumatic", "acute stress", "adjustment disorder" (see appendix p 4 for complete search strings). We also inspected references from the most recent systematic reviews and meta-analyses.[3,4,10,11] Peer-reviewed publications in Dutch, English, German, Italian, Romanian, and Spanish were considered.

See Online for appendix

Eligible studies were randomised controlled trials comparing a CBM intervention to a control condition or to another form of CBM for anxious or depressive symptom outcomes measured on validated clinical scales, in adults aged 18 years and older whose primary complaint consisted of symptoms of anxiety or depression, either diagnosed with a diagnostic interview (eg, structured clinical interview for DSM-IV) or a validated clinical scale (eg, Liebowitz Social Anxiety Scale), or of subclinical intensity evaluated on a validated clinical scale. Participants with comorbid anxious or depressive symptoms were eligible. Disorders were defined according to the DSM-IV or DSM-IV-text revised, as recruitment in most trials probably predated DSM-5. Combination studies of CBM and another intervention were eligible, provided the control group also received the ancillary intervention. Studies contrasting CBM with non-CBM active interventions (eg, cognitive behavioural therapy) were

	Description
Approach and avoidance training	Participants are instructed to either push a joystick towards the computer screen away from themselves to make the presented stimuli smaller and disappear (avoid condition), or pull the joystick away from the screen towards themselves to magnify the presented stimuli (approach condition)
ABM	Participants are typically presented with pairs of words or faces (neutral or threatening) and are trained to direct their attention away from the threatening stimulus by situating the probe in the position of the neutral or positive word or face whenever it was paired with a threatening one; there are many variations in terms of stimuli type (eg, faces, words, other images), and the timing and location of their presentation, as well as tasks used for training, (eg, dot-probe, visual search task)
ABM and CBMI	A combination of ABM and CBMI, usually delivered in the same session
CBMI	Participants are typically presented with ambiguous situations (often realistic scenarios capturing situations occurring in daily life) and are trained to resolve them to favour neutral or positive interpretations over negative interpretations; most CBMI paradigms target the broad range of disorder-relevant situations and cognitions, although some have a very specific focus (eg, interpretations of one specific kind of situation or behaviour)
Opposite ABM	The same as ABM, except that participants are trained to direct their attention toward the threatening stimulus
Opposite CBMI	The same as CBMI, except that participants are trained to resolve the ambiguous situations to favour negative interpretations
Sham training for approach and avoidance training	Typically, the same as approach and avoidance training, except that there is no contingency between pushing or pulling the joystick and the emotional valence of the stimuli, or the stimuli have no emotional valence
Sham training for ABM	Typically, the same as ABM, except that there is no contingency between probe location and the presented stimuli: in 50% of trials the probe replaces neutral or positive words or faces and in 50% of trials the probe replaces negative words or faces
Sham training for CBMI	Typically, the same as CBMI, except that the ambiguous situations are not consistently positively resolved (how exactly this is operationalised varies, but often an ambiguous scenario is resolved to favour positive or benign interpretations in one half of the trial and negative interpretations in the other half); or the ambiguous situations have no emotional valence for the participants
Waitlist	Participants are assigned to a waitlist for the duration of the study and offered the intervention after the active treatment group

ABM=attention bias modification. CBMI=cognitive bias modification-interpretation.

Table 1: **Description of typical cognitive bias modification interventions and control conditions**

excluded. State measures of anxiety or negative mood were ineligible because they do not reliably index symptoms of clinical importance.

Two researchers (LAF and RG) independently screened all abstracts, subsequently examined full texts, and selected eligible randomised controlled trials. All disagreements were resolved by discussion and consultation with a third author (IAC) until consensus was reached. Protocol changes are detailed in the appendix (p 4).

Data extraction

We extracted information about: (1) the sample, including clinical (diagnosed) and subclinical (elevated symptoms); (2) total number of participants randomly assigned; (3) CBM intervention as in approach and avoidance training, ABM, CBMI (definitions in table 1); (4) control condition, including sham training, opposite ABM, waitlist (table 1); (5) number of CBM sessions; (6) delivery, including laboratory, home, clinic, or combinations; (7) outcome measures for anxiety and depression; and (8) publication year.

We expected trials to use multiple outcome measures; hence we prespecified a hierarchy. For studies reporting both anxiety and depression outcomes, we first considered the investigator-declared primary outcome. If none was identified, we selected it based on the focus of the intervention (eg, anxiety outcomes for anxiety disorders). Clinician-based instruments were favoured over self-report, if available.

As anxiety and depression have a high likelihood of comorbidity,[12] we also considered outcomes for comorbid depression in trials of CBM for anxiety disorders and anxiety in trials of CBM interventions for depressive disorders.

We used the risk of bias assessment tool, developed by the Cochrane Collaboration,[13] which assesses possible sources of bias in randomised controlled trials. The following domains were rated: random sequence generation; allocation concealment; masking of participants and personnel; masking of outcome assessors; incomplete outcome data; and selective outcome reporting. Masking of participants and personnel was considered low risk if masking of participants was attempted, regardless of whether subsequent checks were done to establish if it was maintained. For masking of outcome assessors, clinician-based measures were prioritised. For self-report, participants were considered their own assessors,[13] with ratings of low risk given if they were masked to the intervention received. Incomplete outcome data were assessed as low risk if all randomly assigned participants were included in the analysis, through use of an intention-to-treat approach or complete data availability. Selective outcome reporting was assessed as low risk if primary and secondary outcomes were prespecified in a prospectively registered protocol or trial registration, with no substantial changes between registration and publication. Retrospectively registered or non-registered studies were rated as unclear.

Two independent researchers (LAF, RG) extracted outcome data and rated risk of bias, with disagreements resolved by consensus after discussion with another author (IAC).

Data analysis

Means, SDs, and sample sizes in each group were used to calculate between-groups effect sizes as post-intervention standardised mean differences (SMDs) and corresponding 95% CIs. The SMD represents the difference in means between the intervention and control groups divided by the pooled SD. Intention-to-treat data were preferred, when available. For studies with two or more groups from the same category (ie, a type of CBM or of control), we extracted data from those most similar to the standard version. For example, if a study contained both CBMI and a modified version of it with additional components, we chose the former. If data were insufficient for effect size calculations, study authors were contacted. We used multivariate random effects

meta-analysis with a restricted maximum likelihood estimator to do four network meta-analyses (one per outcome). We graphically represented results as network plots, whereby the size of the nodes is directly proportional to the number of patients, while the thickness of the lines connecting the nodes is weighted by the number of trials directly assessing the comparison. Additionally, we constructed network plots that incorporated risk of bias for each domain rated, using coloured edges to represent low, high, and unclear risk of bias. The comparison-specific bias level was set as the rating in most studies in each comparison (ie, the mode).[14]

The transitivity assumption was evaluated by visually inspecting relevant study characteristics. On the basis of previous literature, we considered two potential effect modifiers (number of sessions and delivery setting) and examined their distributions across comparisons. Network consistency, the extent to which included studies are comparable, both statistically and substantively,[15] was evaluated with three methods. First, to detect significant overall inconsistency, we used a design-by-treatment interaction model with a global Wald statistic, which under consistency follows a χ^2 distribution.[16–18] Non-significant p values indicate no inconsistency. Second, we used a loop-specific approach to estimate the inconsistency factor in each loop as the absolute difference between direct and indirect estimates and truncating the CIs to 0, using a Z-test to decide if inconsistency was significant[19] (ie, the lower limit of the inconsistency factor's 95% CI touches 0). Thirdly, we used a side-splitting method,[16] a frequentist adaptation of the original hierarchical Bayesian method.[18,20] It reports the estimated direct and indirect treatment effects and their difference, with consistency inferred based on the p value for the difference.

Contribution plots displayed the differential contributions of direct comparisons to the network summary effect. Interventions were ranked by calculating the surface under the cumulative ranking (SUCRA), which denotes the probability (in percentages) of superior effectiveness for each intervention compared with a theoretical ideal (ie, always the best without uncertainty) intervention.

Heterogeneity was investigated by displaying forest plots, including summary effects along with their 95% CIs and their corresponding 95% prediction intervals for all comparisons. Prediction intervals represent CIs of the approximate predictive distribution of the future trial, considering heterogeneity.[21] We did three further sensitivity analyses excluding studies: (1) using approach and avoidance training, initially devised for addiction[22]; (2) on participants with post-traumatic stress disorder, in which better outcomes were reported for sham than for ABM[23]; and (3) in which participants in the sham intervention were not exposed to any contingency (eg, neutral scenarios). We used network restricted maximum likelihood meta-regression[24] with *mvmeta* to examine two possible moderators for the comparison between CBM and sham—number of treatment sessions (continuous) and delivery setting (recoded dichotomously as laboratory *vs* others).

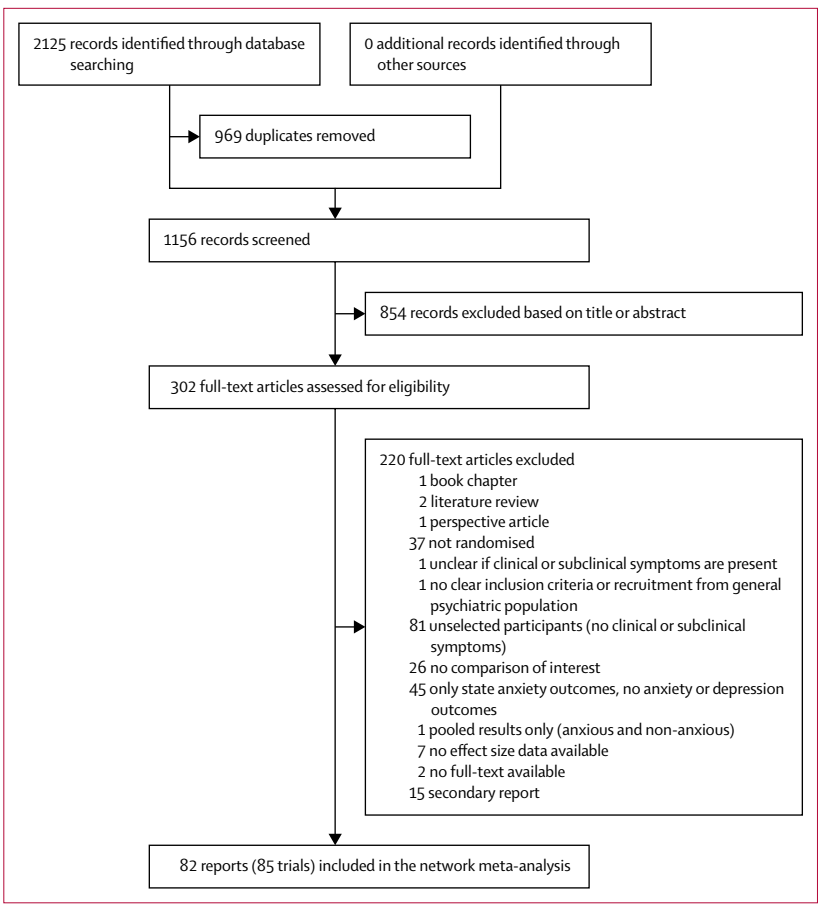

Figure 1: **Study selection**

Small study effects were examined through visualisation of comparison-adjusted funnel plots and with Egger's linear regression test of funnel plot asymmetry.[25] Interventions were ordered such that all active interventions were contrasted sequentially to waitlist, sham, and opposite ABM control conditions.[14]

All analyses were done in STATA/SE version 15[26] (*network* and *mvmeta*[14,16,24]) and R[27] (*netmeta*[28]). The meta-analysis was prospectively registered with PROSPERO, CRD42018086113, and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for network meta-analyses.[29]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

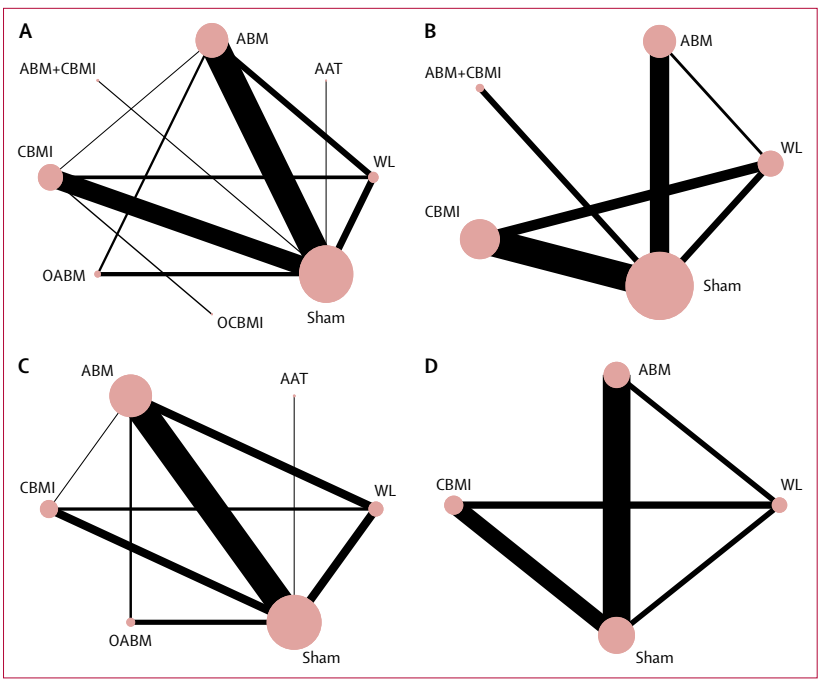

Figure 2: **Network geometry of CBM interventions**
Outcomes are shown for anxiety (A), depression (B), comorbid depression (C), and comorbid anxiety (D). The size of the nodes is directly proportional to the number of patients, while the thickness of the lines connecting the nodes is weighted by the number of trials directly assessing the comparison. AAT=approach and avoidance training. ABM=attention bias modification. CBMI=cognitive bias modification-interpretation. OABM=opposite ABM. OCBMI=opposite CBMI. WL=waitlist.

Results

The search generated 2125 records (1156 after duplicate removal). We excluded 854 records based on abstract inspection, and examined 302 full texts. The PRISMA flowchart[30] (figure 1) shows the inclusion process and the appendix (pp 12–21) reports the studies excluded with reasons. We contacted authors of eight studies with insufficient effect size data and retrieved datasets for one. Consequently, 82 reports describing 85 separate trials were included in the network meta-analysis.

Detailed characteristics of included studies are described in the appendix (pp 22–30). 65 trials (n=2026 treated and n=1871 control participants) focused on anxiety-related disorders of clinical or subclinical intensity. 20 trials (n=544 treated and n=572 control participants) focused on depressive disorders or symptoms. Delivery settings included the laboratory (n=44 studies), online or at home (n=21), clinic or hospital (n=8), or a combination of these (n=12). Treatment sessions ranged from one to 84, with 12 randomised controlled trials using one session, and 43 randomised controlled trials using eight sessions or more. Most trials used sham training and directly compared ABM and sham (figure 2). Comorbid depression outcomes were reported in 31 studies (n=1101 treated and n=1070 control participants) on anxiety disorders. Conversely, comorbid anxiety outcomes were present in 11 studies on depressive disorders (n=250 treated and n=251 control participants).

For the primary outcome of anxiety, the network plot (figure 2A) showed a well connected network, consisting of eight nodes (appendix p 51 for contribution plot). Most direct comparisons were at unclear risk of bias, except for blinding of outcome assessment (unclear or high) and incomplete outcome data (low; appendix p 52). Across methods, there was no evidence for inconsistency (appendix pp 10, 34, 53). In the network meta-analysis (table 2, appendix p 54), only CBMI significantly reduced anxiety compared with waitlist (SMD –0·55, 95% CI –0·91 to –0·19) or sham (SMD –0·30, –0·50 to –0·10). However, prediction intervals for these comparisons were large and included 0. SUCRA probabilities indicated that approach and avoidance training and CBMI presented the greatest likelihood of reducing anxiety outcomes (both around 77%; appendix p 55). Egger's test did not detect funnel plot asymmetry (t[80] 0·31; p=0·76; appendix p 56).

For the primary depression outcome, the network plot (figure 2B) shows a well connected network of CBM interventions, except for the ABM and CBMI combination. Across all methods, there was evidence for inconsistency (appendix pp 10, 35, 57). Risk of bias, the contribution plot, and SUCRA probabilities are presented in the appendix (pp 58–60). In the network meta-analysis (table 3, appendix p 61), CBMI significantly reduced depression compared with waitlist (SMD –0·63, 95% CI –1·04 to –0·23). The 95% prediction intervals were large and included 0 (appendix p 61). Other significant differences involved the singly connected ABM and CBMI node (appendix p 10). Egger's test detected funnel plot asymmetry (t[22] –2·10; p=0·047; appendix p 62).

For the secondary outcome of comorbid depression (in anxiety randomised controlled trials), the network plot (figure 2C) showed a well connected network of CBM interventions, consisting of six nodes. None of the methods revealed evidence of inconsistency (appendix pp 10, 36, 63). Risk of bias, the contribution plot, and SUCRA probabilities are displayed in the appendix (pp 64–66). In the network meta-analysis (appendix pp 37, 67), only CBMI significantly reduced depression compared with waitlist (SMD –0·42, 95% CI –0·68 to –0·15), sham (SMD –0·21, –0·41 to –0·01), and ABM (SMD –0·24, –0·46 to –0·01). However, all 95% prediction intervals were large and, except for CBMI versus waitlist, included 0. Egger's test did not detect funnel plot asymmetry (t[42] –1·34; p=0·19; appendix p 68).

For the secondary outcome of comorbid anxiety in depression randomised controlled trials, the network plot (figure 2D) evidenced a well connected network of CBM interventions, consisting of four nodes. Most comparisons were at unclear and high risk of bias (appendix p 69). Evidence for inconsistency was mixed, with two of the three methods indicating inconsistency (appendix pp 10, 38, 70). The contribution plot and SUCRA probabilities are displayed in the appendix (pp 71–72). The network meta-analysis showed no

	AAT	ABM	ABM and CBMI	CBMI	Opposite ABM	Opposite CBMI	Sham
ABM	–0·46 (–1·50 to 0·58)	..	..	..	..	..	..
ABM and CBMI	–0·45 (–1·71 to 0·81)	0·01 (–0·75 to 0·77)	..	..	..	..	..
CBMI	–0·21 (–1·25 to 0·83)	0·25 (–0·00 to 0·51)	0·24 (–0·52 to 1·01)	..	..	..	..
Opposite ABM	–0·65 (–1·77 to 0·47)	–0·19 (–0·64 to 0·26)	–0·20 (–1·06 to 0·66)	–0·44 (–0·92 to 0·05)	..	..	..
Opposite CBMI	–0·04 (–1·43 to 1·35)	0·42 (–0·53 to 1·38)	0·41 (–0·78 to 1·61)	0·17 (–0·75 to 1·09)	0·61 (–0·43 to 1·65)	..	..
Sham	–0·51 (–1·54 to 0·51)	–0·05 (–0·22 to 0·12)	–0·06 (–0·80 to 0·68)	–0·30* (–0·50 to –0·10)	0·14 (–0·30 to 0·58)	–0·47 (–1·41 to 0·47)	..
Waitlist	–0·76 (–1·85 to 0·32)	–0·30 (–0·68 to 0·08)	–0·31 (–1·13 to 0·51)	–0·55* (–0·91 to –0·19)	–0·11 (–0·68 to 0·45)	–0·72 (–1·71 to 0·26)	–0·25 (–0·61 to 0·10)

Data are standardised mean differences and 95% CIs. Negative values favour the intervention in the column, positive values the intervention in the row. AAT=approach and avoidance training. ABM=attention bias modification. CBMI=cognitive bias modification-interpretation. *Significant standardised mean differences.

Table 2: **Relative treatment effects for all possible pairwise comparisons estimated in the network meta-analysis for anxiety outcomes**

significant differences (appendix pp 39, 73). Egger's test did not detect funnel plot asymmetry (t[11] 0·74; p=0·47; appendix p 74).

Most trials had uncertain or high risk of bias for five of six domains (appendix pp 31, 50). Four randomised controlled trials had low risk of bias for all domains, while six randomised controlled trials had low risk for five domains. Sequence generation was rated low risk in 31 trials (42 had insufficient information), allocation concealment in 13 trials (67 insufficient information), and masking of participants and personnel in 37 trials (38 unclear). Masking of outcome assessors was rated low risk in 39 trials (69 used self-report measures exclusively). For incomplete outcome data, 54 studies reported intention-to-treat analyses or complete outcome data were available. For selective outcome reporting, 12 studies were rated low risk.

Post-hoc sensitivity analyses closely replicated the main analyses (appendix pp 10–11), with a few differences. With the exclusion of post-traumatic stress disorder trials (n=7), ABM significantly reduced anxiety compared with waitlist (SMD –0·35, 95% CI –0·59 to –0·12) and sham (SMD –0·16, –0·28 to –0·04). Excluding trials where sham participants were not exposed to any contingency (n=15), CBMI significantly reduced anxiety compared with waitlist (SMD –0·62, 95% CI –1·07 to –0·18), but not sham.

Meta-regression analyses showed that the number of treatment sessions was not significantly related to outcomes (appendix p 48). Delivery setting was a significant moderator only for the ABM versus sham comparison (β=0·44, 95% CI 0·10–0·77) for anxiety outcomes (appendix p 49).

	ABM	ABM and CBMI	CBMI	Sham
ABM and CBMI	0·55 (–0·23 to 1·33)	..	..	..
CBMI	0·16 (–0·29 to 0·60)	–0·40 (–1·17 to 0·38)	..	..
Sham	–0·10 (–0·43 to 0·23)	–0·65 (–1·36 to 0·05)	–0·26 (–0·57 to 0·06)	..
Waitlist	–0·48 (–1·00 to 0·04)	–1·03* (–1·86 to –0·20)	–0·63* (–1·04 to –0·23)	–0·38 (–0·81 to 0·06)

Data are standardised mean differences and 95% CIs. Negative values favour the intervention in the column, positive values the intervention in the row. ABM=attention bias modification. CBMI=cognitive bias modification-interpretation. *Significant standardised mean differences.

Table 3: **Relative treatment effects for all possible pairwise comparisons estimated in the network meta-analysis for depression outcomes**

Discussion

In a network meta-analysis of 85 trials, CBM interventions showed few benefits over control conditions, for both anxious and depressive symptomatology. In 65 trials in participants with anxiety, CBMI outperformed waitlist (SMD –0·55, 95% CI –0·91 to –0·19) or sham training (SMD –0·30, –0·50 to –0·10) for anxiety outcomes. However, prediction intervals were large and contained an SMD of 0, suggesting that the effects of future similar trials could fluctuate across a wide range of effects. Similar results were reported for comorbid depression outcomes, present in around half of the trials, suggesting that the effects of CBMI might be disorder-specific rather than symptom-specific. These effects are modest compared with similarly delivered internet-based cognitive behavioural interventions for anxiety disorders (SMDs compared with mostly waitlist control ranging from 0·70 for generalised anxiety disorder to 1·31 for panic disorder).[31] In post-hoc analyses excluding the more inert type of sham (neutral scenarios), only differences between CBMI and waitlist remained significant. Few differences emerged among CBM interventions, except for the superiority of CBMI over ABM for comorbid depression.

For ABM, the only significant findings consisted of small effects compared with waitlist and sham on primary anxiety outcomes, in sensitivity analyses excluding post-traumatic stress disorder trials. Our definition of anxiety

disorders predated the DSM-5, hence included stress-related disorders (all included post-traumatic stress disorder trials relied on the DSM-IV-text revised). More generally, findings for ABM corroborate previous meta-analyses reporting very similar estimates,[3,4] but contradict others reporting larger effects of ABM for participants with clinical anxiety.[5,6] A pairwise meta-analysis of 11 studies[5] showed moderate effects of ABM for clinician-rated (SMD 0·42, 95% CI 0·18–0·66), but not self-reported, anxiety. In an individual participant data meta-analysis of 13 trials,[6] the authors reported significant effects of ABM on diagnostic remission (odds ratio 2·57, 95% CI 1·31–5·22), but not on the continuous measure, clinician-administered Liebowitz Social Anxiety Scale. Laboratory delivery was associated with better outcomes for ABM versus sham, corroborating previous reports.[3,4]

In the considerably fewer trials on participants with depression (n=20 trials), only CBMI outperformed waitlist for primary depression outcomes (SMD –0·63, 95% CI –1·04 to –0·23). However, because of evidence of network inconsistency, this finding might be unreliable. The network geometry revealed one open, singly connected, node for the ABM and CBMI combination. Aside from a direct comparison with sham, the whole evidence for the combined intervention was indirect, rendering the very large effects observed not credible. Hence, the effectiveness of the combined treatment cannot be established. We used a hierarchy of outcomes, favouring the investigator-declared primary outcomes and, barring that, clinician-based over self-report measures. Therefore, it is unlikely that our findings are explained by the choice of measures. Importantly, anxiety trials formed well connected networks for both anxiety and depression outcomes, with no evidence for inconsistency, making fundamental differences between trials unlikely and further supporting the robustness of the findings.

Few differences emerged among the various control conditions used. Waitlist was always nominally inferior to sham CBM, supporting the notion that interventions should be compared with more adequate, active control groups.[32] By contrast, a strength of CBM trials is the frequent inclusion of a sham condition, in which participants are not encouraged to preferentially process a specific stimulus type. Analogous to pill placebo, these active control conditions can be targeted (50:50 ratio of targeted *vs* non-targeted emotional stimuli) or just consist of neutral stimuli. Attempts to mask participants to their group allocations contribute to rendering the sham condition similar to placebo, a rare occurrence in research on psychological interventions. Yet just less than half of the trials specifically mentioned participant masking, with an almost equal number lacking information. Therefore, it is difficult to ascertain whether the sham condition truly remained as such. In post-hoc sensitivity analyses excluding studies using the neutral version of sham as control, CBMI was only superior to waitlist. Finally, although sham training does not ostensibly encourage preferential processing, it might nonetheless have beneficial emotional effects[33] by repeatedly exposing participants to bias contingencies and enhancing, for example, psychological flexibility.[34] Nonetheless, pill placebo is also often not inert.[33] Furthermore, some trials included a seemingly paradoxical opposite intervention (ie, opposite ABM), in which contingencies are modified so that negative stimuli are preferentially attended to or processed, in an effort to increase cognitive bias. If the relationship between attention bias and anxiety symptoms is, as hypothesised,[2] causal, this control intervention could be expected to be deleterious, similarly to a nocebo (ie, when a patient's negative expectations result in a more negative effect). Opposite ABM did not diverge from other control conditions; however, because of ethical reasons, few trials used this method.

Our network meta-analysis is not without limitations. For most trials, owing to insufficient information, risk of bias was rated as uncertain across several of the domains considered. The minuscule number of studies with low overall risk precluded us from running further sensitivity analyses. The conduct and reporting of trials of CBM interventions is still wanting, as previously shown.[3] Consequently, as high or unclear risk of bias was associated with exaggerated effect estimates across interventions,[35] the effects reported might overestimate the true effects. Other methods of assessing evidential value[36,37] might complement a more in-depth assessment of trials with uncertain risk. We found little statistical evidence of small study effects in any network. However, publication bias cannot be completely ruled out without directly identifying unpublished trials. We excluded trials in the grey literature such as dissertations and conference proceedings, owing to concerns about insufficient data reporting and reliably connecting these reports with journal articles. For individuals with depression, trials were few and there was evidence of inconsistency in the resultant networks, meaning findings might be unreliable.

As commonly seen in psychological treatment research, heterogeneity is unavoidable. Both ABM and CBMI denote families of approaches targeting a particular process, with variations in the tasks and stimuli used, additional components, and doses. Heterogeneity extends to control conditions, particularly sham training, though most studies used the no contingency (ie, 50:50 ratio) group. For the purposes of the network meta-analysis, sham training conditions were also considered interchangeable across CBM interventions. Although their principle is the same (ie, participants are not encouraged to preferentially process a specific stimulus type), there is variation in the nature of the stimuli (eg, faces in ABM, scenarios in CBMI) or tasks (eg, dot-probe in ABM, ambiguous situations in CBMI) used. We used the random effects model to account for the expected clinical and methodological heterogeneity and we observed no evidence to contradict our assumption in terms of

heterogeneity and inconsistency. Moreover, CBM tasks might differ in reliability and effect on targeted bias. We only investigated two study-level moderators, as, for a meaningful investigation of participant-level moderators, individual participant data would have been required.[38]

The current network meta-analysis aggregates the largest number of CBM trials to date, to our knowledge, and has the unique methodological advantage of simultaneously drawing from direct and indirect comparisons. CBMI emerged as promising and could warrant large-scale testing, ensuring masking of participants and of outcome assessors and avoiding outcome reporting bias. Future trials would also need to clarify whether the intervention should be implemented as stand-alone or added to another, and whether it is cost-effective, given modest benefits observed so far.

CBMI could be construed as a schematic form of cognitive restructuring and it is unclear whether it deals with modifying an actual bias (ie, implicitly) or, rather, prompts participants to explicitly use cognitive restructuring, a core strategy in most cognitive behavioural approaches. Conversely, owing to the already large number of trials and observed small effects, it is doubtful whether further investment in the current dominant ABM paradigms as treatment is justified. This approach might only merit further experimentation in restricted settings with well specified groups of individuals, at least until rigorous, pre-registered pre-clinical studies have tested the reliability and benefits of alternative ABM paradigms.

Contributors

LAF, IAC, and PC were responsible for study concept and design. LAF, RG, ŞS, DD, TAF, and IAC were responsible for acquisition, analysis, or interpretation of data. LAF, RG, and IAC were responsible for statistical analysis. DD and ŞS were responsible for administrative, technical, or material support. PC and TAF were responsible for study supervision. LAF, RG, and IAC were responsible for drafting of the manuscript. PC, ŞS, DD, and TAF were responsible for critical revision of the manuscript for important intellectual content. All authors reviewed the final version of the manuscript.

Declaration of interests

TAF reports personal fees from Mitsubishi-Tanabe and MSD, and a grant from Mitsubishi-Tanabe, outside the submitted work; TAF has a patent 2018-177688 pending. All other authors declare no competing interests.

Data sharing

The datasets generated and analysed during the study, and the code for the network meta-analysis are available on the Open Science Framework.

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